Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to N-Boc Imines and Nitroalkenes

Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to *N*-Boc Imines and Nitroalkenes

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Supporting Information Placeholder

ABSTRACT: A chiral Pd(II)–bis(oxazoline) complex was found to be highly effective in promoting the first direct diastereo- and enantioselective addition of alkylazaarenes to *N*-Boc aldimines and nitroalkenes under mild conditions. Deprotection of Boc-protected products proceeded readily to provide amines in high yields.

Azaarenes and α-stereogenic amines are ubiquitous structures in biologically active pharmaceuticals, agrochemicals, and natural products. Therefore, the development of new catalytic enantioselective methods to construct molecules containing both of these chemotypes should be of significant utility. In this regard, the catalytic enantioselective Friedel–Crafts addition of electron-rich azaarenes (such as indoles and pyrroles) to imines or enamides has been studied extensively.[1] A complementary but currently undeveloped strategy is the direct catalytic enantioselective union of alkylazaarenes with imines or their derivatives (Figure 1). In this reaction, complexation of a chiral metal complex to the nitrogen atom of a C=N moiety within the azaarene can potentially facilitate α-deprotonation of a 2-alkyl substituent under basic conditions to generate a chiral azaallylmetal species[2] that can then undergo stereoselective addition to an imine (Figure 1A). This approach would allow enantioselective access to 2-(*β*-aminoalkyl)azaarenes, substructures that appear in various biologically active drug candidates such as DPP-4 inhibitors[3] and GlyT-1 inhibitors[4] for the treatment of type 2 diabetes and schizophrenia, respectively (Figure 1B).

Although this strategy has not yet, to our knowledge, been realized,[5,6,7,8] encouraging partial progress has been described by the groups of Huang,[9] Rueping,[10] and Kanai and Matsunaga[11] who have reported racemic additions of alkylazaarenes to *N*-sulfonylimines catalyzed by Pd(II),[9a] Sc(III),[9b] or Cu(II)[10,11] complexes (Figure 1C).[12] Also of relevance are racemic Sc(III)-catalyzed Michael additions of alkylazaarenes to enones and an α,β-unsaturated pyrrole,[11,13] and Yb(III)-catalyzed Michael additions of alkylazaarenes to alkylidine malononitriles.[14] While these reports demonstrate important proof of concept, the low acidity of alkylazaarenes means that high temperatures are often required, which may hinder the development of enantioselective variants. Furthermore, the substrates employed were mostly methylazaarenes; when higher alkylazaarenes were employed, poor diastereoselectivities were often obtained.[9a,b,13–15] Finally, in the additions to imines,[9–11] the substrates employed were mainly *N*-tosylimines, and removal of the tosyl group from the products would require strongly reducing conditions that are generally incompatible with sensitive functionality.

Herein, we describe the first catalytic diastereo- and enantioselective additions of 2-alkylazaarenes to *N*-Boc imines. The reactions are promoted by a chiral Pd(II)-bis(oxazoline)complex under experimentally convenient conditions, proceeding at ambient temperature or at 50–60 °C in undried solvent under an air atmosphere. Importantly, deprotection of the amine in the products can be achieved simply by treatment with mild acid. Furthermore, examples of the corresponding additions to nitroalkenes are also provided.

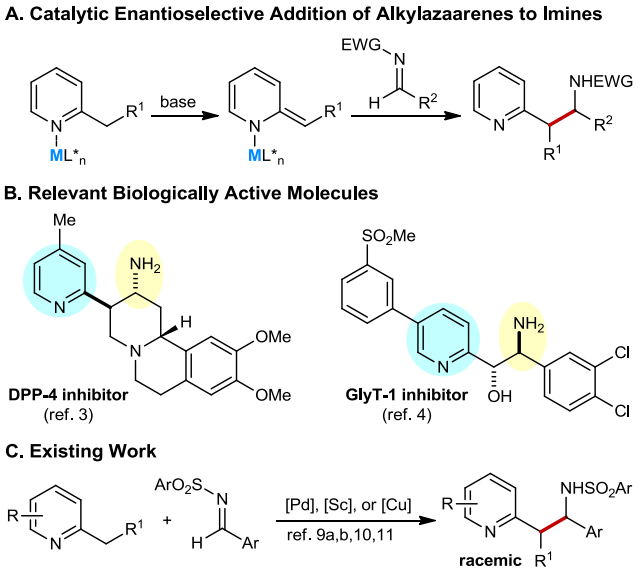
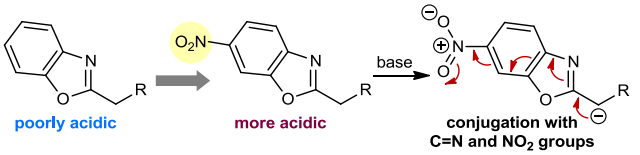


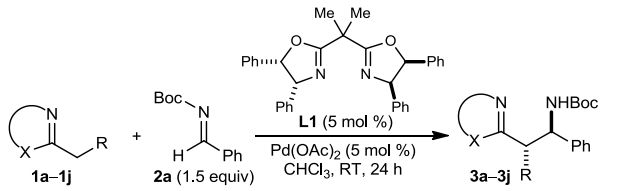
Figure 1. Catalytic additions of alkylazaarenes to imines (1A and 1C) and relevant biologically active molecules (1B).

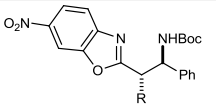
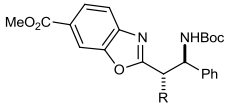
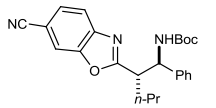
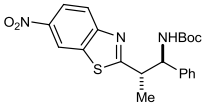
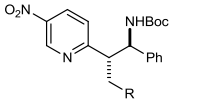
We envisaged that incorporation of an electron-withdrawing group into an azaarene would further acidify the α-protons of a pendant alkyl substituent by stabilization of the conjugate base through conjugation (Scheme 1), allowing deprotonation under conditions that would be much milder than those previously reported[9–11] and hence more suited to enantioselective catalysis.[16] In addition, acidifying groups such as nitro, cyano, or ester substituents would provide highly useful functional handles for subsequent manipulation of the products.



Scheme 1. Strategy for lowering the pK_a of alkylazaarenes.

Table 1. Enantioselective Pd-catalyzed additions of various 2-alkylazaarenes to imine 2a.[a]



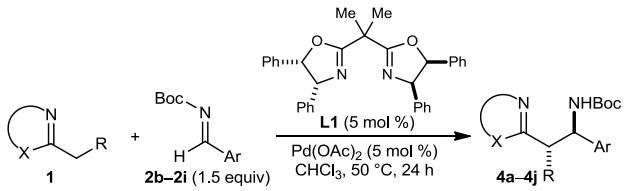
entry	product		yield (%)[a]	dr[b]	ee (%)[c]
1		**3a** R = Me	83[d]	92:8	94 (92)
2		**3b** R = Et	84	>95:5	96
3		**3c** R = *n*-Pr	86	>95:5	97
4		**3d** R = OMe	77[d]	83:17	88 (47)
5[e]		**3e** R = Me	93[d]	86:14	88 (84)
6[e]		**3f** R = *n*-Pr	96	>95:5	95
7[e]		**3g**	98	>95:5	95
8		**3h**	78	91:9	91
9[e,f]		**3i** R = H	70	93:7	88
10[e]		**3j** R = Ph	95	>95:5	98

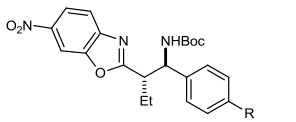
[a] Unless stated otherwise, yields are of pure isolated major diastereomers. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Enantiomeric excesses of the major diastereomer as determined by chiral HPLC analysis. Where indicated, values in parentheses refere to enantiomeric excess of the minor diastereomer. [d] Yield of an inseparable mixture of diastereomers. [e] Reaction conducted at 50 °C. [f] Reaction conducted in THF.

Our investigations began with evaluation of chiral complexes based around metal acetate salts, where it was hoped that the acetate counterions would exhibit sufficient basicity to effect α-deprotonation of an alkylazaarene. Following extensive investigations, we found that the complex composed of $Pd(OAc)_2$ (5 mol %) and a tetraphenyl bis(oxazoline) ligand **L1**[17] (5 mol %) was highly effective in promoting the addition of various alkylazaarenes **1a**–**1j**[18] to *N*-Boc imine **2a** in $CHCl_3$ with high diastereoselectivities (up to >95:5 dr) and enantioselectivities (up to 98% ee) (Table 1). For example, 2-alkyl-6-nitrobenzoxazoles reacted smoothly with **2a** at room temperature to provide products **3a**–**3c** containing methyl, ethyl, or *n*-propyl groups at the α-carbon, respectively (entries 1–3).[19] An α-methoxy substituent on the alkylazaarene was also tolerated, although the ee of the minor diastereomer was only 47% (entry 4). Interestingly, 2-methyl-6-nitrobenzoxazole was not a good substrate as the addition product formed initially underwent a second addition to imine **2a**. The process is not limited to the use of substrates containing nitro groups on the azaarene; substrates containing ester or cyano groups underwent reaction to give products **3e**–**3g**, respectively, in high yields (entries 5–7). While the lower reactivities of these substrates required an increase in reaction temperature to 50 °C to obtain high conversions, high stereoselectivities were maintained. Other azaarenes that are tolerated include 6-nitrobenzothiazole (entry 8) and 3-nitropyridine (entries 9 and 10).

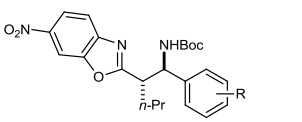
Next, the scope of the process with respect to the imine was studied (Chart 1). Pleasingly, a range of aromatic *N*-Boc

Chart 1. Enantioselective Pd-catalyzed additions of 2-alkylazaarenes to various imines.[a]

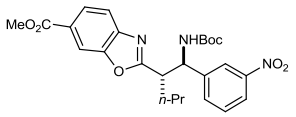




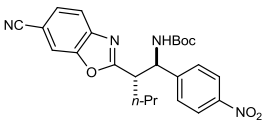
4a[b] R = CN, 87%, >95:5 dr, 87% ee
4b[b] R = NO_2, 93%, >95:5 dr, 97% ee



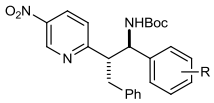
4c[b] R = 4-Me, 86%, 93:7 dr, 84% ee
4d[c] R = 3-Cl, 83%,[d] >95:5 dr, 89% ee[d]
4e R = 2-NO_2, 70%, 77:23 dr, 94% ee



4f 87%, >95:5 dr, 88% ee



4g >95%, >95:5 dr, 91% ee

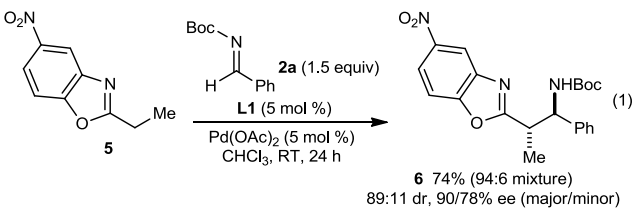


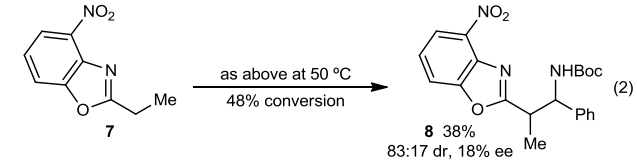
4h R = 4-Br, 84%, >95:5 dr, 98% ee
4i R = 4-CN, 80%,>95:5 dr, >99% ee
4j R = 3-OMe, 94%, 93:7 dr, 93% ee

[a] Unless stated otherwise, yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Reaction conducted at room temperature. [c] Reaction conducted at 60 °C. [d] Yield of a 96:4 inseparable mixture of diastereomers.

aldimines containing various substituents (such methyl, bromo, chloro, nitro, cyano, or methoxy) at the *para* or *meta* positions of the phenyl ring successfully reacted with a number of alkylazaarenes to provide products with high diastereo- and enantioselectivities. An *ortho*-substituted phenyl group on the imine was also tolerated (product **4e**), although the diastereoselectivity was somewhat diminished in this case.

Further experiments were conducted to shed light upon the importance of the position of the electron-withdrawing group on the azaarene. First, the reactivity of 2-ethyl-5-nitrobenzoxazole (**5**) was evaluated, since mesomeric stabilization (−M effect) of the conjugate base of **5** by the 5-nitro substituent is not possible. Surprisingly, **5** underwent efficient coupling with **2a** at room temperature to give **6** as a 94:6 inseparable mixture of diastereomers in 74% yield, with enantiomeric excesses of 90% ee and 78% ee for the major and minor diastereomers, respectively (eq 1). This result demonstrates that in this case, the inductive electron-withdrawing

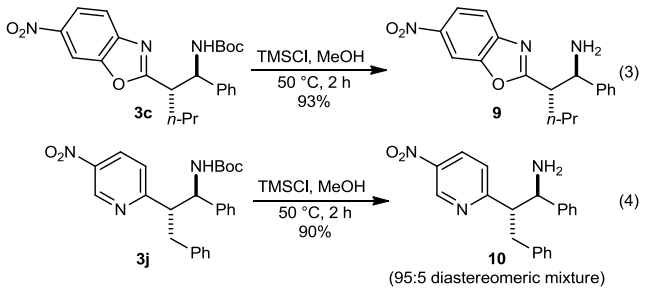




nature of the nitro group (−I effect) is sufficient for good reactivity, and suggests the scope of this process may be significantly broader than presented herein.

In contrast, while 2-ethyl-4-nitrobenzoxazole (**7**) might have been expected to exhibit high reactivity in this process, this substrate provided the product **8** in low yield with poor diastereo- and enantioselectivity (eq 2). Presumably, coordination of the nitro group to the palladium center of the catalyst is responsible for the poor performance of this alkylazaarene.

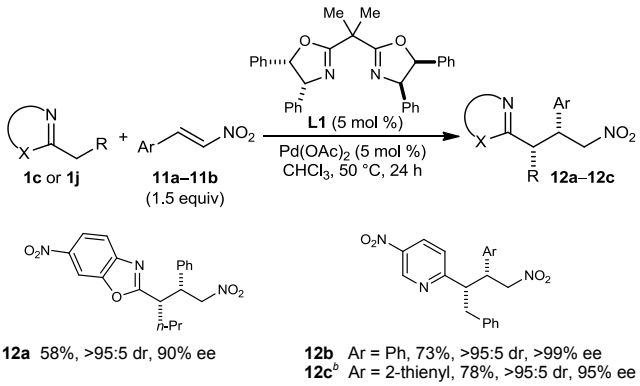
Deprotection of the Boc group from the products was readily accomplished by treatment with HCl in MeOH (generated by dissolving TMSCl in MeOH), as shown by the formation of the amines **9** and **10** from **3c** and **3j** in 93% and 90% yield, respectively (eq 3 and 4). In the case of **10**, very slight erosion in the diastereochemical purity was observed (eq 4).



We have found that nitroalkenes are also suitable coupling partners for 2-alkylazaarenes using the same catalyst system.[20] For example, substrates **1c** and **1j** underwent conjugate addition to nitroalkenes **11a** or **11b** to provide **12a–12c** as single diastereomers with high enantioselectivities (Chart 2).[19]

To investigate the role of the acetate counterions in this process, the reaction of Table 1, entry 1 was repeated using $Pd(TFA)_2$ in place of $Pd(OAc)_2$. No reaction occurred, indicating that the basicity of the counterion is crucial for reactivity.[21] An analogous experiment using $Pd(OBz)_2$ gave **3a** in 90% yield, 74:26 dr, and 87/94% ee (major/minor). Furthermore, a similar experiment using $Pd(OPiv)_2$ gave **3a** in 38% yield,

Chart 2. Enantioselective Pd-catalyzed additions of 2-alkylazaarenes to nitroalkenes.[a]



[a] Yields are of isolated compounds. Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Reaction conducted at 60 °C for 48 h.

56:44 dr, and 80/90% ee (major/minor). The dependence of both the diastereo- and enantioselectivity on the counterion suggests that the carboxylate is involved in the stereoselectivity-determining step.[21] Presumably, one carboxylate remains bound to palladium throughout the reaction.

On this basis, Figure 2 presents a tentative stereochemical model for these reactions. Deprotonation of the alkylazaarene by an acetate ligand of complex **13** leads to species **14**, in which the azaallyl ligand possesses *E*-stereochemistry to minimize steric interactions between the R-substituent and the other ligands. Approach of the imine toward the azaallyl ligand is likely to occur via trajectories approximately perpendicular to the ligand plane, to allow binding/activation of the imine at an axial coordination site. In species **14**, approach of the imine from the top face is relatively unhindered. In species **15**, however, in which the azaallyl ligand adopts an alternative conformation, approach of the imine from the top face is hindered by the acetate ligand, whereas approach from the bottom

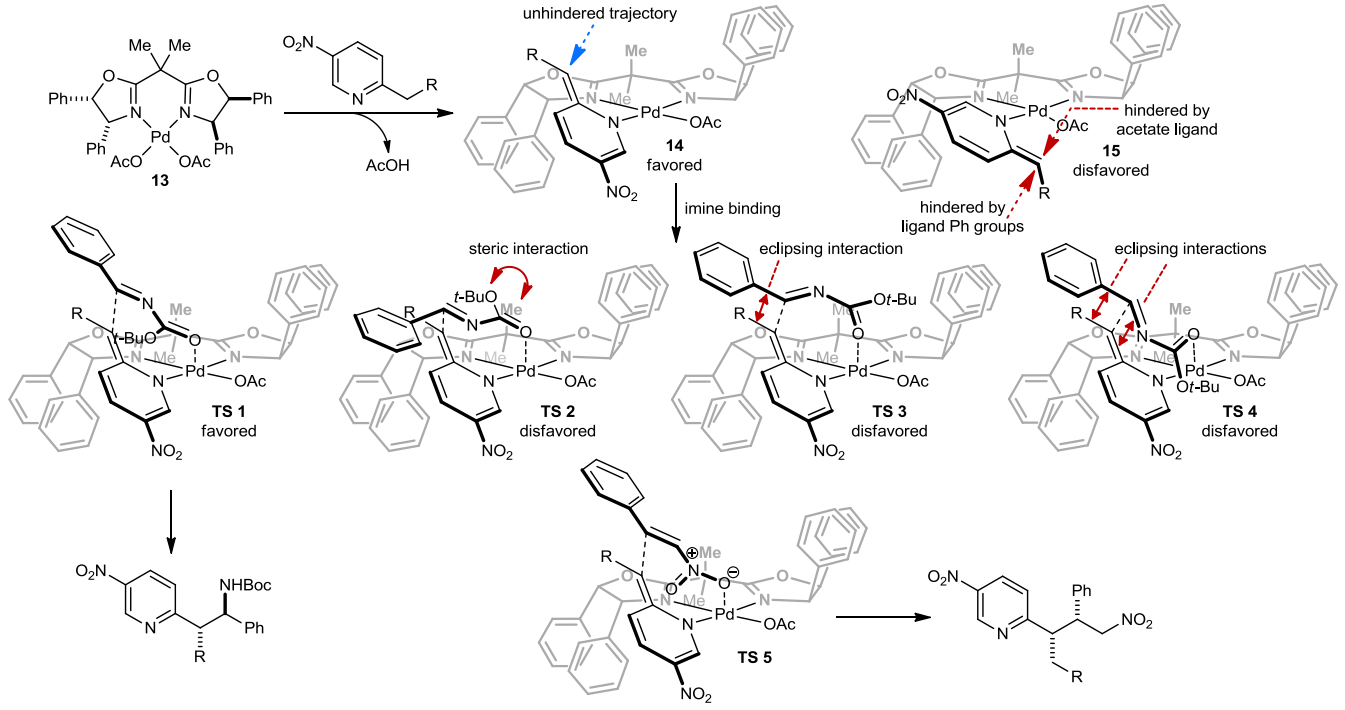
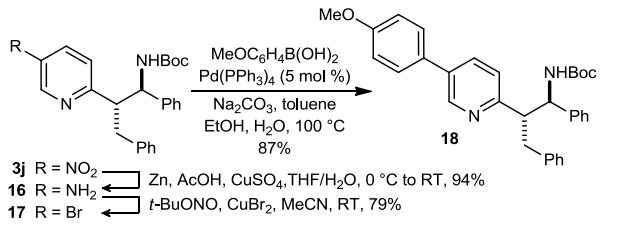


Figure 2. Stereochemical model.

face is hindered by the phenyl groups of the chiral ligand.

Four distinct transition state models resulting from conformation **14** can be envisaged. **TS 3** and **TS 4**, in which the imine possesses an s-*cis* geometry, appear to be unfavorable on the basis of their eclipsing interactions. Of the more favorable staggered conformations **TS 1** and **TS 2**, in which an imine s-*trans* geometry is adopted, **TS 2** is likely to disfavored due to the steric clash of the *tert*-butyl group of the imine with one of the methyl groups of the chiral ligand. Therefore, reaction through **TS 1** is favored. Similar arguments can be invoked to explain the stereochemical outcome of the nitroalkene additions, through **TS 5**.

Finally, to demonstrate the synthetic utility of the products, **3j** was converted into biaryl **18** by a sequence involving nitro group reduction, conversion of the resulting amine **16** into bromide **17**, and Suzuki–Miyaura coupling (Scheme 2).



Scheme 2. Manipulation of product **3j**.

In conclusion, we have described the first catalytic enantioselective additions of alkylazaarenes to *N*-Boc imines and nitroalkenes. Under the action of a chiral Pd(II)–bis(oxazoline) complex, the reactions proceed with high levels of diastereo- and enantioselection. By exploiting the acidifying effect of nitro, cyano, or ester groups on the azaarene, the reactions occur under mild, experimentally convenient reaction conditions (undried solvent, air atmosphere, and often ambient temperature). In the case of the imine addition products, deprotection of the Boc group is readily accomplished to reveal the corresponding amines. This work lays the foundation for the development of further catalytic enantioselective addition reactions of alkylazaarenes for the production of novel chiral azaarene-containing building blocks. Studies in this area are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In one case, a good diastereomeric ratio of 9:1 was obtained by the Rueping group. See ref. 10.

(16) For amine-catalyzed racemic addition of 3,5-diethyl-4-nitroisoxazole to carbonyl compounds, see: Adamo, M. F. A.; Suresh, S. *Tetrahedron* **2009**, *65*, 990-997.

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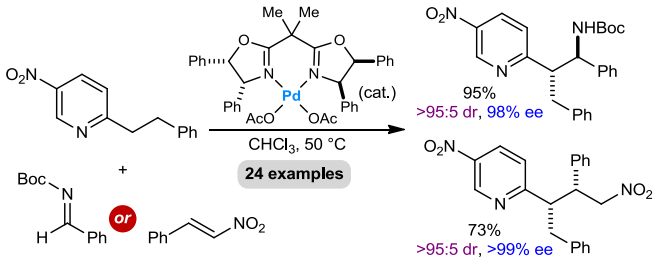
(18) See Supporting Information for the structures of **1a**–**1j**.

(19) The relative and absolute configurations of the products obtained herein were assigned by analogy with those of **3j**, **9**, and **12b** which were determined by X-ray crystallography using a copper radiation source. See Supporting Information for details.

(20) For reviews of nitroalkenes as conjugate acceptors, see: (a) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751-762. (b) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95-127. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894.

(21) Repeating the reaction of Table 1, entry 1 using $Pd(TFA)_2$ in place of $Pd(OAc)_2$, in the presence of Et_3N (10 mol %) gave **3a** in 32% conversion, 95:5 dr, and 88/44% ee (major/minor).


Me
Me
O
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Ph
Ph
N
N
Ph
Pd
Ph
(cat.)
AcO
OAc
O_2N
N
Ph
$CHCl_3$, 50 °C
24 examples
+
Boc
N
H
Ph
or
Ph
NO_2
O_2N
NHBoc
N
Ph
95%
>95:5 dr, 98% ee
Ph
O_2N
Ph
NO_2
N
73%
>95:5 dr, >99% ee
Ph